b) determining the order of said plurality of genomic DNA fragments in the genome;

c) determining the sequence of selected regions of said plurality of genomic DNA fragments; and

d) identifying nucleotides in said plurality of genomic DNA fragments which vary between individuals, thereby defining a set of biallelic markers.

87. The method of Claim 86, further comprising selecting a minimally overlapping set of genomic fragments from said nucleic acid library.

88. The method of Claim 86, further comprising identifying one biallelic marker per genomic DNA fragment.

89. The method of Claim 86, further comprising identifying two or more biallelic markers per genomic DNA fragment.

90. The method of Claim 86, further comprising detecting a set of biallelic markers having a desired average heterozygosity rate.

91. The method of Claim 86, further comprising selecting biallelic markers having a heterozygosity rate of at least about 0.18.

92. The method of Claim 86, further comprising selecting biallelic markers having a heterozygosity rate of at least about 0.32.

93. The method of Claim 86, further comprising selecting biallelic markers having a heterozygosity rate of at least about 0.42.

94. The method of Claim 86, wherein said identifying step comprises identifying at least about 20,000 biallelic markers.

95. The method of Claim 86, wherein the step of determining the sequence of selected regions of said plurality of genomic DNA fragments comprises inserting fragments of said plurality of genomic DNA fragments into a vector to generate a plurality of subclones and determining the sequence of a region of the inserts in said plurality of subclones or a subset thereof.

96. The method of Claim 86, wherein a set of about 10,000 to about 30,000 genomic DNA inserts with an average size between 100kb and 300kb are ordered.

97. The method of Claim 86, further comprising determining the position of said biallelic markers along the genome or a portion thereof.

98. The method of Claim 86, further comprising obtaining pluralities of biallelic markers such that each marker is in linkage disequilibrium with at least one of identified markers.

99. The method of Claim 86, wherein said portion of the genome comprises at least 200 kb of contiguous genomic DNA.

100. The method of Claim 86, wherein said portion of the genome comprises at least 2 Mb of contiguous genomic DNA.

101. The method of Claim 86, wherein said portion of the genome comprises at least 20 Mb of contiguous genomic DNA.

102. The method of Claim 86, further comprising the step of identifying one or more groups of biallelic markers which are in proximity to one another in the genome.

103. The method of Claim 86, further comprising the step of identifying one or more groups of biallelic markers which are in proximity to one another in the genome, wherein the biallelic markers in each of these groups are located within a genomic region spanning from 1 to ~~5kb~~.

104. The method of Claim 86, further comprising the step of identifying one or more groups of biallelic markers which are in proximity to one another in the genome, wherein the biallelic markers in each of these groups are located within a genomic region spanning from 50 to 150kb.

105. The method of Claim 86, further comprising the step of identifying one or more groups of biallelic markers which are in proximity to one another in the genome, wherein the biallelic markers in each of these groups are located within a genomic region spanning more than 1Mb.

106. A set of biallelic markers obtained by the method of Claim 86, wherein the markers in said set are on average evenly spaced over the full genome or a portion thereof.

107. The set of biallelic markers of Claim 106, wherein the markers in said set are ordered relative to one another.

108. The set of biallelic markers according to Claim 106 or Claim 107, wherein the markers in said set have a known genomic position.

109. The set of biallelic markers of Claim 106, wherein said biallelic markers are separated from one another by an average distance of 100 to 150kb.

110. The set of biallelic markers of Claim 106, wherein said biallelic markers are separated from one another by an average distance of 25 to 50kb.

111. The set of biallelic markers of Claim 106, wherein said biallelic markers are separated from one another by an average distance of 10 to 200kb.

a' 112. The set of biallelic markers of Claim 106, wherein said biallelic markers have a heterozygosity rate of at least about 0.18.

113. The set of biallelic markers of Claim 106, wherein said biallelic markers have a heterozygosity rate of at least about 0.32.

114. The set of biallelic markers of Claim 106, wherein said biallelic markers have a heterozygosity rate of at least about 0.42.

115. A map comprising an ordered array of at least 20,000 biallelic markers obtained by the method of Claim 86.

116. A method of identifying one or more biallelic markers associated with a detectable trait comprising the steps of:

a) determining the frequencies of each allele of said one or more biallelic markers obtained by the method of Claim 86 in individuals who express said detectable trait and individuals who do not express said detectable trait; and

b) identifying one or more alleles of said one or more biallelic markers which are statistically associated with the expression of said detectable trait.

117. A method of identifying one or more biallelic markers associated with a detectable trait comprising the steps of:

a) selecting a gene in which mutations result in a detectable trait or a gene suspected of being associated with a detectable trait; and

b) identifying one or more biallelic markers obtained by the method of Claim 86 within the genomic region harboring said gene which are associated with said detectable trait.

118. A method for determining whether an individual is at risk of developing a detectable trait or suffers from a detectable trait associated with said trait comprising the steps of:

a) obtaining a nucleic acid sample from said individual;

b) screening said nucleic acid sample with one or more biallelic markers obtained by the method of Claim 86; and

c) determining whether said nucleic acid sample contains one or more of biallelic markers statistically associated with said detectable trait.

119. A method of using a drug comprising:

a) obtaining a nucleic acid sample from an individual;

b) determining the identity of the polymorphic base of one or more biallelic markers obtained by the method of Claim 86 which is associated with a positive response to treatment with said drug or one or more biallelic markers obtained by the method of Claim 86 which is associated with a negative response to treatment with said drug; and

c) administering said drug to said individual if said nucleic acid sample contains one or more biallelic markers associated with a positive response to treatment with said drug or if said nucleic acid sample lacks one or more biallelic markers associated with a negative response to said drug.

120. A method of selecting an individual for inclusion in a clinical trial of a drug comprising:

a) obtaining a nucleic acid sample from an individual;

b) determining the identity of the polymorphic base of one or more biallelic markers obtained by the method of Claim 86 which is associated with a positive response to treatment with said drug or one or more biallelic markers associated with a negative response to treatment with said drug in said nucleic acid sample; and

c) including said individual in said clinical trial if said nucleic acid sample contains one or more biallelic markers obtained by the method of Claim 86 which is associated with a positive response to treatment with said drug or if said nucleic acid sample lacks one or more biallelic markers associated with a negative response to said drug.

121. A method of identifying a gene associated with a detectable trait comprising the steps of:

a) determining the frequency of each allele of one or more biallelic markers obtained by the method of Claim 86 in individuals having said detectable trait and individuals lacking said detectable trait;

b) identifying one or more alleles of one or more biallelic markers having a statistically significant association with said detectable trait; and

c) identifying a gene in linkage disequilibrium with said one or more alleles.

REMARKS

Page 1 of the Sequence Listing has been amended to provide the names of the inventors as the applicants according to U.S. procedure rather than listing the assignee as the applicant. The remainder of the Sequence Listing is identical to the Sequence Listing in the PCT Application. Accordingly, the amendments to the Sequence Listing do not introduce any new matter.

If the Examiner has any questions regarding the above amendments, he is cordially invited to contact the undersigned so that any such questions may be promptly resolved.

Respectfully submitted,

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Dated: January 14, 2000

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AMEND
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